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Aldrin and Dieldrin: A Reevaluation of the Cancer and Noncancer Dose-Response Assessments

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The dose-response analyses of cancer and noncancer health effects of aldrin and dieldrin were evaluated using current methodology, including benchmark dose analysis and the current U.S. Environmental Protection Agency (U.S. EPA) guidance on body weight scaling and uncertainty factors. A literature review was performed to determine the most appropriate adverse effect endpoints. Using current methodology and information, the estimated reference dose values were 0.0001 and 0.00008 mg/kg-day for aldrin and dieldrin, respectively. The estimated cancer slope factors for aldrin and dieldrin were 3.4 and 7.0 $(mg/kg\text{-}day)^{-1}$, respectively (i.e., about 5- and 2.3-fold lower risk than the 1987 U.S. EPA assessments). Because aldrin and dieldrin are no longer used as pesticides in the United States, they are presumed to be a low priority for additional review by the U.S. EPA. However, because they are persistent and still detected in environmental samples, quantitative risk assessments based on the best available methods are required. Recent epidemiologic studies do not demonstrate a causal association between aldrin and dieldrin and human cancer risk. The proposed reevaluations suggest that these two compounds pose a lower human health risk than currently reported by the U.S. EPA.

KEY WORDS: Aldrin; benchmark dose; dieldrin; dose-response modeling; pesticide

1. INTRODUCTION

Aldrin (CAS No. 309–00–2) and dieldrin (CAS No. 60–57–1) are organochlorine insecticides that were widely used in the United States from the 1950s until 1970. The U.S. Department of Agriculture canceled all uses of aldrin and dieldrin in 1970. On December 2, 1970, the U.S. Environmental Protection Agency (U.S. EPA) was created by executive order, and pesticide registration authority was given to the new agency. In 1972, the U.S. EPA approved the registration of aldrin and dieldrin for termite control. Use of aldrin and dieldrin to control termites continued until the manufacturer voluntarily canceled the registration in 1987.[1] However, because these compounds are environmentally persistent, they can still be detected in samples of soil or groundwater. Recent studies have reported the presence of dieldrin in environmental samples (soil, sediment, and water) decades after the uses of aldrin and dieldrin were discontinued.[2–7] For example, in 2012 the Florida Department of Health detected 0.0020–0.40 μg/L dieldrin in 116 of 287 private drinking water wells sampled in Volusia County.[7]

When quantitative risk assessments are performed or when environmental action levels are established, it is common for the toxicity of target compounds to be based on reference dose (RfD) and/or cancer slope factor (CSF) values derived and provided by the U.S. EPA. The RfD and CSF values for aldrin and dieldrin currently promulgated by the U.S. EPA's Integrated Risk Information System (IRIS) are 20–25 years old.[8–10]

In the 1988 IRIS review of aldrin,[9] the U.S. EPA calculated an oral RfD of 0.00003 mg/kg/day based on a chronic dietary study of aldrin in rats by

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Fitzhugh *et al.*[11] The critical effect was histopathological changes in the liver that were recognized as characteristic "chlorinated insecticide" lesions. The Agency for Toxic Substances and Disease Registry (ATSDR) developed a minimal risk level (MRL) of 0.00003 mg/kg/day for aldrin, based on the same study.[1]

In its 1990 IRIS review of dieldrin, the U.S. EPA calculated an oral RfD of 0.00005 mg/kg/day.[10] This assessment was based on a chronic dietary study in rats by Walker *et al.*[12] The critical effect was increased liver weight and liver-to-body weight ratios; the LOAEL was found to be 1.0 ppm. Histopathological lesions considered characteristic of exposure to an organochlorine insecticide were reported at the 10 ppm dose level. ATSDR also used the Walker *et al.* study to develop a minimal risk level (MRL) of 0.00005 mg/kg/day for dieldrin.[1] The MRL was calculated based on the same reasoning and calculations as the IRIS RfD.

In a 1987 review of aldrin, the U.S. EPA calculated a CSF of 17 $(mg/kg\text{-}day)^{-1}$.[8] This CSF was the geometric mean of two slope factors derived from studies in mice in which dose-related increases in the incidence of liver tumors were observed following chronic oral (dietary) exposure to aldrin.

In a 1987 review of dieldrin, the U.S. EPA calculated an oral CSF of 16 $(mg/kg\text{-}day)^{-1}$.[8] This CSF was the geometric mean of slope factors derived from 13 studies in which liver tumors were observed following chronic oral (dietary) exposure to dieldrin in mice.

The U.S. EPA's methods and guidelines for dose-response analysis have changed since these reviews were performed. Benchmark dose (BMD) modeling is preferred to the use of NOAEL or LOAEL as a point of departure.[13,14] Also, the conversion of dose levels between species and recommendations for uncertainty factors have been revised.[14] Given that aldrin and dieldrin have not been used in the United States for decades, updated reviews of aldrin and dieldrin by the agency are not expected. The persistence of these compounds at detectable levels in environmental samples, however, requires the use of RfDs and CSFs in site-specific risk assessments. Without further evaluation of these compounds by the agency, risk assessors will continue to rely on the U.S. EPA assessments that are now approximately a quarter of a century old.[8–10]

In the current evaluations, dose-response analyses of aldrin and dieldrin were conducted using the U.S. EPA's recommended BMD methods. The objective of this analysis is the derivation of RfD and CSF values based on the current methods and guidelines used by the U.S. EPA.

2. METHODS

2.1. Literature Search

The National Library of Medicine's TOXNET and PubMed databases were searched for studies on aldrin and dieldrin. Particular attention was paid to published studies with subchronic or chronic exposures of aldrin or dieldrin to *in vivo* laboratory models with endpoints relevant to human toxicity. Epidemiological studies were reviewed to identify possible adverse health effects in humans.

2.2. Benchmark Dose

The U.S. EPA's Benchmark Dose Software (BMDS, available from the U.S. EPA) and 2012 Benchmark Dose Technical Guidance document[13] were used for the BMD analyses. For the derivation of RfD values, the dichotomous multistage model was used for analysis of quantal endpoints such as incidence of histopathological lesions, and where applicable, the continuous polynomial model was used for analysis of organ weight data. Tumor incidence data were analyzed with the multistage cancer model to derive CSF values. When an acceptable curve fit of carcinogenicity data could not be achieved with the multistage cancer model, dichotomous Weibull, gamma, and quantal-linear models were applied.

The curve fit to each data set produced by BMDS (version 2.4) was evaluated by the criteria described in the 2012 Benchmark Dose Technical Guidance document. For a model's curve fit to be acceptable, the following criteria must be met:[13,14]

- p-value must be >0.1.
- Scaled residuals report the gap between the curve line and the actual data points; for the model to be acceptable, all scaled residuals must have an absolute value of <2.
- The Akaike information coefficient (AIC) is used for comparison between models; generally, a lower AIC value indicates a better curve fit to the data.
- Even when the numbers indicate a good curve fit, a visual inspection of the graph is important to ensure the curve is not wavy or contains other aberrations.

When it was appropriate to vary the parameters of the BMD analysis of a data set, the guidance was applied to determine the best curve fit and the most accurate values for BMD and 95% lower confidence limit of BMD ($BMDL_{05}$). The BMD was based on a 10% benchmark response for each analysis.

2.3. Dose Conversions

The animal exposure levels were entered into the BMDS spreadsheet as human equivalent dose (HED) levels in units of mg/kg-day. The two steps in estimating the HED from the animal dose are conversion of the dietary concentrations to mg/kg-day in the animals and conversion of the animal dose to the equivalent human dose. The first step (conversion of the dietary concentrations) assumed the following: rats (both sexes), 1 ppm in diet = 0.05 mg/kg-day; male mice, 1 ppm in diet = 0.17 mg/kg-day; female mice, 1 ppm in diet = 0.18 mg/kg-day.[9,10,15] The second step used the "¾ power" assumption where the HED (mg/kg body weight per day) is equal to the animal dose × (animal body weight/human weight)$^{1/4}$.[14,16,17] The animal body weight was estimated at 0.45 kg for rats, 0.0373 kg for male mice, and 0.0353 kg for female mice; the human body weight was assumed to be 70 kg.[9,10,14]

3. RESULTS

3.1. Noncancer BMD Analyses

3.1.1. Aldrin

A thorough literature search for toxicity studies of aldrin was performed, and the 1964 study by Fitzhugh *et al.*[11] was determined to be the best available study, and liver toxicity was the most sensitive endpoint identified. Twelve rats/sex/group were fed diets containing 0, 0.5, 2, 10, 50, 100, or 150 ppm (0.025, 0.1, 0.5, 2.5, 5, 7.5 mg/kg-day) aldrin for two years. Signs of liver toxicity, including enlarged centrilobular hepatic cells, with increased cytoplasmic oxyphilia, and peripheral migration of basophilic granules were reported at dose levels ≥0.5 ppm (0.025 mg/kg-day). The authors described these effects as characteristic "chlorinated insecticide" lesions. Liver-to-body weight ratios were significantly higher than controls in all aldrin treatments ($p < 0.05$), but the effect was not dose dependent at the lower dose levels.

The incidence of "characteristic chlorinated pesticide changes" in the livers of aldrin-treated rats are quantal data and can be modeled by the dichotomous multistage model in the BMDS program.[20] The total of all lesions associated with chlorinated pesticide at each dose level were entered into the model, which produced a curve fit that met the acceptance criteria regarding *p*-value, scaled residual, and AIC. The calculated BMD for aldrin-induced liver lesions in rats was 0.0234 mg/kg-day. The $BMDL_{05}$ was 0.0121 mg/kg-day. The mean liver weight to body weight ratio data were not amenable for a BMD analysis by the continuous multistage model, because the model requires means to be accompanied by standard deviations. The Fitzhugh *et al.*[11] paper did not report the standard deviations associated with the respective mean relative organ weights.

3.1.2. Dieldrin

After a thorough literature search of toxicity studies on dieldrin, the study by Fitzhugh *et al.*[11] was determined to be the best available study, and liver toxicity was the most sensitive endpoint identified. Fitzhugh *et al.* reported the results of chronic toxicity studies for both aldrin and dieldrin and is the same publication used to derive the BMD and $BMDL_{05}$ values for aldrin. The liver lesions seen in dieldrin-treated rats were similar to those seen following chronic dietary exposure to aldrin.

A dichotomous multistage model was used to analyze the incidence of "characteristic chlorinated pesticide changes" in the livers of dieldrin-treated rats. As described in the BMD analysis of aldrin above, the total incidence of all lesions associated with chlorinated pesticide at each dose level were entered into the model, and the resulting curve fit met the acceptance criteria. The BMD was 0.0137 mg/kg-day, and the $BMDL_{05}$ was 0.00837 mg/kg-day.

As with the aldrin data set described above, the dieldrin study reported that relative liver weights increased with dieldrin exposure, but the data were not amenable to BMD modeling because the standard deviations were not reported.

3.1.3. Reference Dose Levels

Uncertainty factors are used to reduce the dose level at the point of departure to account for uncontrolled or unknown variables in the development of a RfD value. The uncertainty factors in the current evaluation include the following:

- A factor of 10 was applied to account for intraspecies variability (the range of sensitivity within the human population), as quantitative information for evaluating toxicokinetic and toxicodynamic differences among humans are not available.
- An interspecies uncertainty factor of $10^{0.5}$ was applied because HED scaling was used to extrapolate oral doses from rats to humans. Although the HED scaling addresses some aspects of cross-species extrapolation of toxicokinetic and toxicodynamic processes, some residual uncertainty remains. In the absence of chemical-specific data to quantify this uncertainty, U.S. EPA's HED guidance recommends use of an uncertainty factor of $10^{0.5}$.[16,17]
- The ATSDR[1] identified a data need for a well-conducted developmental toxicity study of aldrin and/or dieldrin. No human studies are available on developmental effects for any exposure route. Animal studies that examined the ability of aldrin and dieldrin to cause reproductive or developmental effects have reported conflicting results with effects only reported at moderate-to-high dose levels. The quality of those studies was determined to be questionable in U.S. EPA and ATSDR reviews.[1,18] Thus, an uncertainty factor of $10^{0.5}$ was applied to account for database deficiency due to lack of a reliable developmental toxicity study.[14]

After dividing the respective $BMDL_{05}$ values by the total uncertainty factor of 100 ($= 10 \times 10^{0.5} \times 10^{0.5}$), the estimated RfD values are 0.0001 mg/kg-day for aldrin and 0.00008 mg/kg-day for dieldrin. Table I summarizes the data used to derive BMD-based RfD values for aldrin and dieldrin.

3.2. BMD-Based CSFs

3.2.1. Aldrin

A thorough literature search identified only one chronic oral carcinogenicity study of aldrin that was amenable to BMD modeling. The National Cancer Institute (NCI) 1978 data set[19] included a control group and two treatment dose levels that showed a dose-dependent increase in liver tumor incidence in mice.

Tumor incidence data are recommended by U.S. EPA[20] for use in the dichotomous multistage-cancer model. This model allows for variation of the degree of polynomial to find the best curve fit. In a data set containing two treatment dose levels, the degree of polynomial can be set to either 1 or 2. With the degree of polynomial set to 1, the resulting curve had a good visual fit, and the mathematical tests for fit produced values within the acceptable ranges. The second run produced a curve that failed one of the acceptability criteria (p value). Thus, the first run (degree of polynomial = 1) was deemed to have the better curve fit. The CSF value calculated for the NCI 1978 male mouse liver tumor incidence data is 3.4 $(mg/kg\text{-}day)^{-1}$. Table II summarizes the data used to derive a BMD-based CSF value for aldrin.

3.2.2. Dieldrin

A thorough literature search identified five oral carcinogenicity data sets for dieldrin that were amenable to BMD modeling. These included studies by Walker *et al.*,[21] which provided four data sets, and one data set NCI 1978.[19]

Walker *et al.*[21] presented results of two chronic dieldrin experiments in CF1 mice. In one experiment, male and female mice were exposed to 0, 0.1, 1, or 10 ppm dieldrin in diet for 132 weeks; in the other, male and female mice were exposed to 0, 1.25, 2.5, 5, 10, or 20 ppm dieldrin in diet for 128 weeks. The NCI[19] study exposed male and female B6C3F1 mice to 0, 2.5, or 5 ppm dieldrin in diet for 80 weeks. The female mice in the NCI study did not show a dose-related increase in liver tumor incidences; thus only the male mice data were analyzed.

As stated above, the dichotomous multistage cancer model[20] allows for variation of the degree of polynomial to find the best curve fit. If an adequate curve fit cannot be created by variation of the degrees of polynomial, this may be because the program is trying to fit the curve to the higher dose groups, whereas the focus in BMD modeling should be in the range of the lower dose levels. It is therefore sometimes allowable to exclude data at the highest dose level(s) in order to get an acceptable curve fit at the lower dose levels.[13,20] However, at least two dose levels above control must remain in the data set.

Below are summaries of output results used to determine the best-fitting curve and the best BMD-derived cancer slope value for each data set.

The 132-week male mouse tumor incidence data from Walker *et al.*[21] was analyzed with degree of polynomial set both to 2 and to 3. Both models produced acceptable curve-fit evaluation results. Based on the comparison of AIC values, the model with

Table I. Data Input and Output for BMD-Based Derivation of RfD Values for Aldrin and Dieldrin

	Rat dose (mg/kg-day)	Human equivalent dose (mg/kg-day)	Incidence of lesions/ number examined	Degrees of freedom	BMD (mg/kg-day)	$BMDL_{05}$ (mg/kg-day)	UF[a]	RfD[b] (mg/kg-day)
Aldrin	0	0	1/17	3 or 4	0.023	0.012	100	0.0001
	0.025	0.0071	4/19					
	0.1	0.028	9/19					
	0.5	0.14	11/22					
	2.5	0.71	18/18					
	5	1.4	11/11					
	7.5	2.1	9/9					
Dieldrin	0	0	1/17	4	0.014	0.0084	100	0.00008
	0.025	0.0071	4/22					
	0.1	0.028	11/23					
	0.5	0.14	11/18					
	2.5	0.71	20/20					
	5	1.4	18/18					
	7.5	2.1	11/11					

[a]Uncertainty factor (UF) = 100, representing 10 for human variability, $10^{0.5}$ for interspecies variability, and $10^{0.5}$ for lack of a reliable developmental toxicity study.
[b]RfD = $BMDL_{05}$/UF.

Table II. Data Input and Output for BMD-Based Derivation of CSF Value for Aldrin

Mouse dose (ppm)	Human equivalent dose (mg/kg-day)	Incidence of tumors/ number examined	Degrees of freedom	BMD (mg/kg-day)	$BMDL_{05}$ (mg/kg-day)	CSF $(mg/kg\text{-}day)^{-1}$
0	0	3/20	1	0.043	0.029	3.4
4	0.12	16/49				
8	0.25	25/45				

Data source was NCI 1978.[19]

the degree of polynomial set to 3 provided the better curve fit. The BMD-derived CSF for 132-week male mouse tumor incidence data from Walker *et al.* is 9.6 $(mg/kg\text{-}day)^{-1}$.

The 132-week female mouse tumor incidence data from Walker *et al.*[21] was analyzed with degree of polynomial set to 1, 2, or 3 with the full data set or to 1 or 2 with the highest dose level excluded. None of the models produced a curve with an acceptable fit to the data set. These data were also analyzed using the Weibull, gamma, and quantal-linear models in the BMDS software (version 2.4), but none of these models produced a curve that met the acceptance criteria. Thus, a BMD-derived CSF was not calculable for this data set.

The 128-week mouse tumor incidence data from Walker *et al.*[21] were analyzed in the BMDS program. The complete data set with degree of polynomial, respectively, set to 1, 2, 3, or 4 produced the exact same curve, and the curve-fit acceptance criteria were not met. The tumor incidence in each sex dose dependently increased up to 5 ppm and then decreased at 10 and 20 ppm. This decrease in tumor incidence at the higher dose levels is likely due to the higher mortality rates at these dose levels, thus the dose-response curve for tumor incidence had an irregular shape. Removal of the highest dose level (20 ppm) did not improve the curve fit in either sex. However, removal of the top two dose levels (10 and 20 ppm) produced a curve with acceptable curve-fit results, and degree of polynomial values set to 2 or 3 produced identical results within each sex. The BMD-derived CSFs from the 128-week mouse tumor incidence data by Walker *et al.* are 5.9 $(mg/kg\text{-}day)^{-1}$ for males and 8.0 $(mg/kg\text{-}day)^{-1}$ for females.

The 80-week male mouse tumor incidence data from NCI 1978[19] were analyzed in the BMDS program. The first model (degree of polynomial = 1) produced a curve with a good visual and mathematical fit. Although the second model (degree

of polynomial = 2) provided a visually perfect fit to the data points, the *p*-value was "NA." Based on these factors, the first model is deemed to have the better curve fit, and the CSF for the NCI 1978 male mouse liver tumor incidence data is 5.3 $(mg/kg\text{-}day)^{-1}$.

Based on the geometric mean of the four individual BMD-derived CSF values described above, the overall CSF value for dieldrin is 7.0 $(mg/kg\text{-}day)^{-1}$. Table III summarizes the data used to derive a BMD-based CSF value for dieldrin.

4. DISCUSSION

4.1. Noncancer Endpoints

At the time of the 1988 and 1990 U.S. EPA reviews of aldrin and dieldrin, the use of BMD modeling to determine point of departure was not in common practice. Under the current U.S. EPA guidelines, BMD modeling is preferred to the NOAEL/LOAEL approach if the available data support appropriate use of the model. In the current review, liver lesion data for chronic dietary exposure to aldrin and dieldrin provided in the Fitzhugh *et al.*[11] study were modeled using BMDS software provided by the U.S. EPA. The resulting $BMDL_{05}$ values, with appropriate uncertainty factors applied, produced RfD values of 0.0001 mg/kg-day for aldrin and 0.00008 mg/kg-day for dieldrin.

4.1.1. Decisions and Impacts During the RfD Derivation for Aldrin

The U.S. EPA RfD for aldrin is based on the study by Fitzhugh *et al.*[9,11] In this study, rats were fed diets containing 0.5–150 ppm (0.025–7.5 mg/kg-day) for two years. The original study's authors described the liver lesions that they observed at all dose levels as "characteristic of chlorinated insecticide poisoning." These included enlarged centrilobular hepatic cells (hypertrophy), with increased cytoplasmic oxyphilia, and peripheral migration of basophilic granules. Using the total incidences of these same endpoints, the current BMD-based analysis derived a RfD value of 0.0001 mg/kg-day for aldrin, which is approximately three-fold higher than the LOAEL-derived RfD of 0.00003 mg/kg-day.

This review of noncancer effects of aldrin used the same data set and critical endpoint from the same study as used by the U.S. EPA.[9] Each step of the current RfD derivation contributed to the differences with the U.S. EPA estimate. Without the HED adjustment, the $BMDL_{05}$ is 0.0426 mg/kg-day in the current review, which is 70% higher than the LOAEL of 0.025 mg/kg-day identified by the U.S. EPA.[9] The current review applied a HED factor of 0.28 [derived from (0.45 kg rat body weight/70 kg human body weight)$^{\frac{1}{4}}$ per current U.S. EPA guidance[16,17]] to adjust the dose from rat to human; an interspecies dose adjustment was not done in the U.S. EPA review.[9] The HED factor reduced the $BMDL_{05}$ to 0.012 mg/kg-day, which is about half of the value of the LOAEL. The application of uncertainty factors, 1,000 (10× for extrapolation from animals to humans, 10× for in the range of human sensitivities, and 10× because the RfD is based on a LOAEL rather than a NOAEL) in the U.S. EPA review versus 100 in the current review, reversed the relative positions of the RfD values to indicate three times less potency in the current review versus the previous review. Overall, the method for identification of critical effect level and the uncertainty factors widened the gap between the current and previous RfD values of aldrin, while the HED adjustment reduced that difference.

4.1.2. Decisions and Impacts During the RfD Derivation for Dieldrin

A study by Walker *et al.*[12] is the basis of the U.S. EPA RfD[10] and the ATSDR chronic MRL (oral)[1] for dieldrin. In their reviews of the Walker *et al.* study, the U.S. EPA and ATSDR identified 0.1 ppm (0.005 mg/kg-day) dieldrin as the NOAEL and 1 ppm (0.05 mg/kg-day) as the LOAEL. The critical effect was increased liver weight in female rats. The hepatic lesions observed at 1 ppm were not considered by the authors of the Walker *et al.*[12] paper to be associated with organochlorine insecticides. Therefore, the LOAEL of 1 ppm determined by U.S. EPA[10] and ATSDR[1] is based solely on increased liver weights in female rats.

Increased liver weight without other signs of liver toxicity (e.g., histopathology or clinical chemistry), however, is considered an adaptive response to increased metabolism of the chemical and is generally not considered to be an adverse effect.[22–25] The U.S. EPA has determined that increased liver weight and hepatoctyte hypertrophy were adaptive nonadverse effects in the IRIS toxicological reviews of chlordane, vinyl chloride, and cumene.[26–28] Thus, the NOAEL of the Walker *et al.*[21] study would

Table III. Data Input and Output for BMD-Based Derivation of CSF Value for Dieldrin

Reference for data set (subjects)	Mouse dose levels (ppm)	Human equivalent dose (mg/kg-day)	Percent with tumors/ number examined	Degrees of freedom	BMD (mg/kg-day)	BMDL (mg/kg-day)	BMD-based CSF $(mg/kg\text{-}day)^{-1}$
Walker *et al.*	0	0	20%/288	1	0.020	0.010	9.6
(132-week male	0.1	0.0026	26%/124				
CF1 mice)[25]	1.0	0.026	31%/111				
	10	0.26	94%/94				
Walker *et al.*	0	0	13%/297	–[a]	–	–	–
(132-week female	0.1	0.0026	27%/90				
CF1 mice)[25]	1.0	0.026	37%/87				
	10	0.26	92%/148				
Walker *et al.*	0	0	12%/78	2	0.032	0.017	5.9
(128-week male	1.25	0.033	20%/30				
CF1 mice)[25]	2.5	0.065	43%/30				
	5.0	0.13	87%/30				
	10.0	0.26	45%/11[b]				
	20.0	0.52	71%/17[b]				
Walker *et al.*	0	0	10%/78	1	0.022	0.013	8.0
(128-week female	1.25	0.032	17%/30				
CF1 mice)[25]	2.5	0.065	43%/28				
	5.0	0.13	60%/30				
	10.0	0.26	53%/17[b]				
	20.0	0.52	38%/21[b]				
NCI 1978	0	0	15%/20	1	0.027	0.019	5.3
(80-week male	6.1	0.077	33%/49				
B6C3F1 mice)[19]	13.8	0.15	54%/46				
Geometric mean of four BMD-based cancer slope factors							7.0

[a]No curve fit was achieved with the Walker *et al.* 132-week female mouse tumor incidence data.
[b]The two highest dose levels (10 and 20 ppm) were excluded from the analyses of the Walker *et al.* 128-week male and female data sets.

more appropriately be 1 ppm (0.05 mg/kg-day), and the LOAEL should be 10 ppm (0.5 mg/kg-day) where the increased liver weights were accompanied by histopathological changes (parenchymal cell changes including focal hyperplasia). Compared to the Walker *et al.* study, the study by Fitzhugh *et al.*[11] appears to provide the more sensitive endpoints for hepatic lesions associated with chronic dieldrin exposure.

Without the HED factor, the $BMDL_{05}$ derived from Fitzhugh *et al.*[11] was 0.0296 mg/kg-day, which is nearly six times higher than the LOAEL of 0.005 mg/kg-day identified by the U.S. EPA.[10] With application of the HED factor of 0.28, the $BMDL_{05}$ was adjusted to 0.0084 mg/kg-day, which is still higher than the LOAEL value. An adjustment for HED was not used on the LOAEL in the U.S. EPA review.[10] Although there were differences in selection of specific uncertainty factors, the total uncertainty factor applied in each review was 100. The RfD of 0.00008 mg/kg-day in the current review is 60% higher than the previous value of 0.00005 mg/kg-day.[10] The element that had the greatest influence on the disparity between the current and previous dieldrin reviews was the selection of study used to identify the critical effect. Because different data sets were used, the influence of BMDL versus LOAEL as a point of departure is immaterial. As with aldrin, the application of the HED factor reduced the RfD value by about one-third. The uncertainty factor was identical in both reviews, so it had no role in the difference.

4.1.3. Concordance with International Assessments of Aldrin and Dieldrin

The Joint WHO/FAO Meeting on Pesticide Residues (JMPR) considered aldrin and dieldrin interchangeable, due to the rapid biotransformation of aldrin to dieldrin in mammalian systems.[33] JMPR identified 0.5 ppm dieldrin as the NOAEL in the Fitzhugh *et al.*[11] study, noting that the authors of the study classified the hepatic lesions seen at 0.5 ppm as "trace or minimal." JMPR affirmed this NOAEL with a dog study[30] in which a diet including 1 ppm

dieldrin produced enlarged livers with no histopathological changes. These nontoxic dose levels in the rat and dog studies were both determined by JMPR to be equivalent to 0.025 mg/kg-day, to which JMPR applied an uncertainty factor of 250 to derive an allowable daily intake (ADI) of 0.0001 mg/kg-day for aldrin and dieldrin combined.[29,31] An explanation uncertainty factor of 250 was not provided in the JMPR review.

The BMD-based RfD values derived in the current review are similar to the ADI for aldrin and dieldrin endorsed by JMPR.[31,32] This ADI is used for drinking water guidelines of the World Health Organization,[33] Australian National Health and Medical Research Council,[34] the New Zealand Ministry for the Environment,[35] and formerly by Health Canada.[36] Health Canada does not currently publish a drinking water guideline for aldrin and dieldrin, as these compounds are no longer found in Canadian drinking water supplies at levels that could pose a risk to human health.[37]

4.2. Updated Noncancer Literature Search

Five new animal studies of dieldrin were identified. Four of the five animal studies investigated the effects of dieldrin on perinatal development. Cameron *et al.*[38] and Foster[39] each exposed mice to a range of dieldrin doses by oral gavage during gestation and lactation, and both studies showed no effects on birth outcomes. Although the offspring in the Cameron *et al.*[38] study developed mammary tumors, the strain of mice used was genetically predisposed to develop mammary tumors. The Richardson *et al.*[40] study exposed mice to dieldrin perinatally and evaluated specific neurotoxic effects not measured in most developmental toxicity studies. Tarraf *et al.*[41] gave rats a single intraperitoneal injection of dieldrin in late-gestation and found effects on dam mammary gland maturation and effects on litter size and pup weight gain. The California EPA[42] determined in 2007 that liver toxicity in adult animals was a more sensitive endpoint than developmental toxicity when assessing noncancer risk of dieldrin at school sites in California. A nondevelopmental study by Hallegue *et al.*[43] investigated the hepatotoxic effects of dieldrin, and the results were consistent with the known hepatotoxicity in studies previously reviewed by U.S. EPA[10] and ATSDR.[1] Overall, none of the recent studies provides a more sensitive endpoint for aldrin or dieldrin than the liver toxicity reported by Fitzhugh *et al.*[10]

Fourteen noncancer epidemiologic studies of aldrin and/or dieldrin were identified from the PubMed search of epidemiologic literature published since 1987 and not included in the 2002 ATSDR review. These studies have evaluated a variety of potential endpoints including Parkinson's disease,[44–46] diabetes,[47,48] monoclonal gammopathy of undetermined significance (MGUS),[49] age at menopause,[50] thyroid hormones,[51] cryptorchidism,[52] infant's length of gestation, birth weight, and crown-heel length,[53] Leydig cell disruption,[54] lymphocyte subsets,[55] and allergic immune response in women and infants.[56] In general, these studies either showed no effect or provided conflicting results.

4.3. Cancer Endpoints

4.3.1. Decisions and Impacts During the CSF Derivation for Aldrin

The U.S. EPA's[8] oral CSF for aldrin of 17 $(mg/kg\text{-}day)^{-1}$ is the geometric mean of three slope factors derived from linearized multistage modeling of the chronic dietary mouse studies by Davis[57,58] and NCI 1978.[19] The Davis study provided two CSF values, one for each sex. The current review included only the NCI study to derive a CSF value of 3.4 $(mg/kg\text{-}day)^{-1}$.

Factors that contributed to the lower CSF value in the current review of aldrin include exclusion of the Davis[57,58] data sets, the use of BMD modeling, and the method of HED adjustments. The U.S. EPA[8] analysis of the Davis data sets provided CSF values of 23 $(mg/kg\text{-}day)^{-1}$ for female mice and 18 $(mg/kg\text{-}day)^{-1}$ for male mice. BMD modeling requires a control and at least two treatment dose levels.[13] Because the Davis[57,58] study used only one treatment dose level, this study does not lend itself to BMD analysis. Furthermore, the dose level (10 ppm) was purposely selected to be high enough to produce tumors and may overestimate the cancer risk at lower dose levels. With a control and two dose levels (4 and 8 ppm), the NCI 1978[19] study provides an adequate study design for BMD modeling.

The method for determination of point of departure (linearized multistage versus BMD modeling) was a factor in the difference between the current and previous CSF values. In the U.S. EPA review,[8] a linearized multistage model of the NCI[19] tumor incidence data produced a CSF value of 12 $(mg/kg\text{-}day)^{-1}$. When the same data set was applied to BMD

modeling in the current review, the CSF value was 3.4 $(mg/kg\text{-}day)^{-1}$, indicating lower cancer risk for aldrin.

The method for adjusting dose levels between mice and humans has been revised since the previous review. The U.S. EPA[8] used a HED factor of 0.08 based on the ratio of mouse to human body weights to the 1/3 power. Consistent with current U.S. EPA[16,17] guidance, the scaling factor in the current review is 0.15 based on the ratio of mouse to human body weights to the 1/4 power. Thus, application of the current HED factor increased the estimated BMD and $BMDL_{05}$ values and lowered the CSF value.

4.3.2. Decisions and Impacts During the CSF Derivation for Dieldrin

In its 1987 review of dieldrin carcinogenicity, the U.S. EPA[8] derived an oral CSF of 16 $(mg/kg\text{-}day)^{-1}$ based on the geometric mean of 13 individual CSFs. These CSF values ranged from 7.1 to 55 $(mg/kg\text{-}day)^{-1}$. The slope factors were derived from studies in mice in which dose-related increases in the incidence of liver tumors were observed following chronic dietary exposure to dieldrin. Among the 13 data sets were Davis (male and female C3H mice),[57,58] Thorpe and Walker (male and female CF1 mice),[59] Tennekes *et al.* (male CF1 mice),[60] and Meierhenry *et al.* (male mice of the C57B1/6J, C3H/He, and B6C3F1 strains).[61] Because each of these studies tested only one dose level (10 ppm in diet), these eight data sets are not amenable to BMD modeling. Studies by Walker *et al.*[21] and NCI 1978[19] each included a control group and two or more treatment dose levels and thus were used for the BMD modeling in the current review.

The reduced number of data sets, the use of BMD modeling, and the method of HED adjustments each contributed to the lower CSF value in the current review of dieldrin. Some of the data sets that were not applicable to BMD modeling contributed high cancer risk values for dieldrin in the U.S. EPA review. The data set reported in the 132-week dietary exposure to female CF1 mice[21] was applied to several BMD models (multistage-cancer, Weibull, quantal-linear, and gamma) with and without the highest dose, but a curve that met the acceptance criteria was not achieved. If an acceptable curve had been found, the impact this data set may have had on the final geometric mean of the individual CSF values is not known. The BMD models attempted with the132-week female CF1 mouse data produced CSF values of 11–18 $(mg/kg\text{-}day)^{-1}$. If these data were included in the geometric mean of the individual CSF values, the overall CSF value would be 7.7–8.5 $(mg/kg\text{-}day)^{-1}$. However, each of these curve models failed the acceptance criteria[13,20] by having a p value that was too low (<0.1) and a highest scaled residual value that was greater than 2. Thus they cannot be included in the overall CSF value with confidence.

The BMD-derived CSF values for three of four data sets were lower than the corresponding CSF values derived by the linearized multistage procedure. The 128-day dietary exposure to female CF1 mice reported by Walker *et al.*[21] generated a BMD-derived CSF value of 8.0 $(mg/kg\text{-}day)^{-1}$, which is slightly higher than the 7.1 $(mg/kg\text{-}day)^{-1}$ derived by the U.S. EPA.[8] This example demonstrates that a BMD model does not always result in a lower CSF value than a linearized multistage model.

As described above in the discussion of the CSF for aldrin, the U.S. EPA[8] used a HED factor of 0.08 based on 1986 guidance, and the scaling factor used in the current review was 0.15 based on current U.S. EPA guidance.[16,17] This difference lowers the CSF value in the current review compared to the previous review.

4.3.3. Considerations with Other Assessments of Aldrin and Dieldrin

The only cancer dose response for aldrin and dieldrin is that done by the U.S. EPA in 1987[8] based on liver tumors in mice. It is questionable whether the tumors seen in the mouse are relevant for linear low dose extrapolation to humans. It is generally agreed that aldrin and dieldrin are nongenotoxic.[1,9,10,18] Furthermore, the carcinogenic response has been seen only in mice and not in other laboratory species (rats, hamsters, and dogs).[11,12,19,62,63] Stevenson *et al.*[64] theorized that dieldrin-induced oxidative stress or its sequelae result in modulation of gene expression that favors expansion of initiated liver cells in mice but not in rats. Although a number of cancer epidemiologic studies have been conducted since the U.S. EPA[8] assessment, there is not enough evidence from these studies to conclude that there is a causal association between exposure to aldrin or dieldrin and an increased risk of cancer in humans.

Only the U.S. EPA[8] has classified aldrin and dieldrin as probable human carcinogens. The National Toxicology Program[65] has not classified aldrin or dieldrin as known or probable human carcinogens. The International Agency for Research on Cancer (IARC)[66] has determined that aldrin and dieldrin cannot be classified as to their carcinogenicity. ATSDR does not classify substances as to their carcinogenic potential but its ToxFAQs fact sheet[67] states that: "There is no conclusive evidence that aldrin or dieldrin cause cancer in humans." The World Health Organization[33] has determined that aldrin and dieldrin "make very little contribution, if any, to the incidence of cancer in humans."

Assuming that aldrin and dieldrin are carcinogenic to humans, the methods used in the current dose-response assessment decreased the CSF values from 17 to 3.4 $(mg/kg\text{-}day)^{-1}$ for aldrin and from 16 to 7 $(mg/kg\text{-}day)^{-1}$ for dieldrin, indicating a lower cancer risk than reported by the U.S. EPA.[8] For comparison, the current review of aldrin proposes a lifetime human cancer risk similar to hydrazine or quinolone (CSF = 3.0 $(mg/kg\text{-}day)^{-1}$.[68,69] The proposed lifetime human cancer risk for dieldrin is similar to N-nitrosodi-N-propylamine (CSF = 7.0 $(mg/kg\text{-}day)^{-1}$)[70] and benzo[a]pyrene (CSF = 7.0 $(mg/kg\text{-}day)^{-1}$).[71]

4.4. Updated Carcinogenicity Literature Search

One new animal study related to the carcinogenicity of dieldrin was identified.[38] The authors reported that perinatal exposure to dieldrin promotes tumors in genetically predisposed mice (i.e., mice that were genetically modified to be susceptible to the type of tumor expressed); its relevance to the human experience is questionable.

Twenty-three epidemiologic studies identified in the literature search assessed various cancer outcomes including any cancer,[72,73] lung cancer,[74] Non-Hodgkin's Lymphoma,[75–79] pancreatic cancer, breast cancer,[80–87] childhood cancers,[88] prostate cancer,[86,89] and carcinoma of the gallbladder.[90–93] The self-reported exposure and self-reported disease diagnosis of several of the studies limit their interpretation. Where exposures were measured, they were generally measured in blood or fat after the disease state had already been determined. The only study that measured exposure prior to determination of disease status was the mortality study by Swaen *et al.*[72] and the follow-up mortality study by van Amelsvoort *et al.*[73] These two studies followed a cohort of 570 male employees engaged in the production of aldrin and dieldrin. The workers were first employed between January 1, 1954 and January 1, 1970. Swaen *et al.*[72] determined the vital status through January 1, 2001. Van Amelsvoort *et al.*[73] followed vital status through April 30, 2006. The authors of those studies found no evidence of an increased risk of cancer in the cohort.

5. CONCLUSION

The updated evaluations of the dose-response toxicity and carcinogenicity of aldrin and dieldrin indicate that these compounds are less toxic and carcinogenic than currently reported by the U.S. EPA's IRIS program. The official IRIS values for RfD[9,10] and CSF[8] for aldrin and dieldrin are decades old, whereas the methods in the current evaluation are based on modern BMD analyses and current guidelines for dose extrapolation between species and uncertainty factors. The proposed RfD and CSF values are offered as alternatives to the old IRIS values for application in quantitative risk assessments of exposures of aldrin and dieldrin to human populations. Recent epidemiological and laboratory studies in the published literature raised no new concerns about aldrin or dieldrin that have not already been addressed in the existing reviews by U.S. EPA and ATSDR.

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